Submission to the
Medicines Classification Committee
for the reclassification of:

oseltamivir

(Tamiflu® powder filled capsules, 75mg)

From Prescription Medicine to:

Pharmacist Only Medicine

For:

The treatment and prophylaxis of influenza in adults and adolescents.

January 2005

Sponsor: **Roche Products (New Zealand) Limited**

Executive Summary

This application seeks approval for the reclassification of oseltamivir (Tamiflu®) 75 mg powder filled capsules from Prescription Only Medicine to Pharmacist Only Medicine status for treatment and prophylaxis of influenza in adults and adolescents. The key to appropriate use of Tamiflu is the administration within 48 hours of symptom onset. The requirement for a doctor's prescription makes it difficult for potential influenza sufferers to access Tamiflu in time to commence treatment. Tamiflu is a safe and effective treatment for influenza. The potential public health benefit has not been realised due to the limited window of opportunity for effective treatment. Tamiflu has an excellent safety profile that is consistent and stable with very few adverse characteristics making it appropriate for use as a Pharmacist Only Medicine. Improved access to Tamiflu will compliment the vaccination programme in an inter-pandemic situation and assist in the preparation for an influenza pandemic.

Part A

The international birth date for Tamiflu was 23 September 1999 following registration in Switzerland. Marketing approval for Tamiflu has been granted for the treatment of influenza in adults (75mg twice daily for 5 days) in 76 countries including the USA, Japan, the EU, Switzerland, and many Asian, Middle and South American countries. In 53 of the countries Tamiflu is also indicated for the prevention of influenza in adults and adolescents.

In the United Kingdom, Tamiflu is currently available to be dispensed by Pharmacists to at risk patients. In the UK, a Pharmacist Only Medicine classification does not exist and therefore, Tamiflu is supplied via the NHS Patient Group Directions (PGD). In addition to the UK, the NDPSC of Australia is currently evaluating a submission to reschedule oseltamivir. In all other markets Tamiflu is supplied via prescription.

Tamiflu was granted consent in New Zealand on 27 January 2000 for the treatment of influenza in adults and adolescents. Roche Products (New Zealand) Limited launched the product in the New Zealand market in March 2000. On 5 February 2004, Tamiflu was approved for the prevention of influenza in adults and adolescents. At the date of this submission, Tamiflu has been available on the New Zealand market for 59 months.

Tamiflu is a well-tolerated medicine that currently requires few warnings in order to be safely used. The following warning statements are proposed for the labelling of the Tamiflu Pharmacist Only Medicine pack:

For children consult your Doctor.

Check with your doctor or pharmacist before using Tamiflu if
* you are pregnant or may become pregnant
* are breastfeeding or
* if you suffer from kidney problems.

The proposed statements for the label are consistent with the proposed Tamiflu datasheet.

Part B

INFLUENZA IN NEW ZEALAND

Influenza is a significant public health issue in New Zealand, not only in terms of morbidity and mortality, but in its financial impact, and its potential to overwhelm both primary care and hospital services during epidemics in the winter months.

Between 10% and 20% of New Zealanders (380 000 to 760 000 people) are infected by influenza each year. Vaccination is the principal treatment option for prevention of influenza in New Zealand. However despite efforts to promote annual influenza vaccination and awareness, a significant proportion of older people (24%) still do not take advantage of the free flu vaccination.

The influenza antiviral medicines fall into one of two classes, the M2 inhibitors or the neuraminidase inhibitors, and are distinguished by the mechanism by which they inhibit viral replication.

Tamiflu is the only approved neuraminidase inhibitor available on the New Zealand market. Neuraminidase inhibitors prevent the release of the virus and promote viral aggregation reducing the virus available to infect other cells. The neuraminidase inhibitors are well tolerated, have fewer adverse events than M2 inhibitors such as amantadine and most importantly are active against both influenza A and B.

Efficacy studies show that Tamiflu significantly reduces the burden of influenza in an individual by reducing duration, severity and incidence of complications. It also assists in the prevention of influenza in those who have been exposed to influenza. To ensure effectiveness of Tamiflu, treatment must commence with 48 hours of symptom onset.

Measures to adequately deal with inter-pandemic influenza are critical for enhancing the nation's capacity to deal with pandemic situations i.e. use of vaccines and antiviral medicines.

It has been 35 years since the last influenza pandemic. Global experts including the WHO are warning that it is not a question of if but when the next pandemic will occur and many countries are now developing strategies to cope with the next influenza pandemic.

In 1999 the Influenza Pandemic Planning Committee of the Communicable Diseases Network of Australia and New Zealand devised a Framework for influenza pandemic planning. In October 2002 the Ministry of Health published the Influenza Pandemic Action Plan to provide a framework for preparation and response by the health sector.

The use of antiviral medication prophylactically would be vital for containing the spread of infection until such time as vaccine became available. A number of countries have advocated the stock piling of neuraminidase inhibitors in the event of a pandemic, a position endorsed by WHO. However, it is of vital importance that antiviral medicines are used during the inter-pandemic years to maintain production capacity and distribution supply channels. Inter-pandemic supply will also ensure health care professionals have the experience to administer these drugs and the public are aware of their availability for treatment and protection.

A move to reclassify Tamiflu to Pharmacist Only Medicine resulting in improved access to the product would provide New Zealand with the increase in experience necessary for pandemic preparedness.

CLASSIFICATION ISSUE

Tamiflu is a safe, effective and convenient oral treatment option that compliments the Influenza Vaccination Programme; however treatment must start within the first 48 hours. Accelerated failure time modelling of real influenza data collected in an open-label mutli-centre international study confirmed a strong relationship between the time of intervention and the duration of the illness. In fact, the earlier the treatment began with Tamiflu the shorter the illness duration.

Presenting to the GP to obtain a prescription for Tamiflu is a barrier to access. Although some 21.5 million patients have received Tamiflu since its launch, considering that during a typical influenza season up to 10% of the global population may contract symptomatic influenza, the usage of Tamiflu is low. In the UK, Tamiflu is available under the NHS to elderly and at-risk patients with influenza-like illness within the first 36 hours of symptom onset to enable faster access. In a recent study it was found that only 20% of at risk patients present to their GP in time for treatment, rising to 47% for primary care services that operate “out-of hours”. In Australia, only 50% of influenza patients present to their GP, many preferring to visit the local pharmacy. At present the pharmacist can only

offer symptomatic relief which does nothing to curb the spread of the infection in the patient and to those in contact with the patient.

A study conducted in the UK suggests that patients with self-limiting conditions, seen directly by the community pharmacist, find the service feasible, satisfactory and an acceptable method of delivery. The same study also demonstrated additional benefit in terms of transfer of 38% of the GPs' workload to the community pharmacist.

It is likely that during an influenza outbreak the demand on primary care services would make it even more difficult to obtain an appointment with a GP within the 48 hour timeframe to maximise therapeutic benefit from taking a neuraminidase inhibitor.

As demonstrated above, the timing of Tamiflu treatment is critical, and it is expected that Pharmacist Only Medicine access to Tamiflu will reduce the time to intervention, the duration of illness, and possible transmission to contacts.

THE ROLE OF TAMIFLU

During the development programme, Tamiflu was studied in over 11 000 patients from both the Northern and Southern Hemisphere. The patient treatment pool consisted of adults, elderly / high risk subjects and children aged 1-12 years.

Results of the studies show that Tamiflu significantly reduces the burden of influenza in an individual by reducing duration, severity and the incidence of secondary complications. It is also effective in preventing influenza in those who have contact with an influenza infected individual.

BENEFITS OF TAMIFLU AS A PHARMACIST ONLY MEDICINE

It is widely acknowledged in the literature that neuraminidase inhibitors are important tools for the management of influenza. Part B of the full submission discusses the benefits of reclassifying Tamiflu to a Pharmacist Only Medicine and the considerable public heath benefits of improved access to Tamiflu.

The expected benefits to both the consumer and to the public of Pharmacist Only Medicine access to Tamiflu include:

- **Reduced morbidity**: i.e. reduced spread of influenza infection, and reduced incidence of secondary complications.
- **Reduced antibiotic use for influenza-related complications** during an outbreak and **reduced antibiotic unnecessary demand** from the doctor.

- **Reduced economic cost**: i.e. reduced pressure on primary care services during an outbreak, fewer hospitalizations, and less absenteeism.
- **Potential reduction of deaths from secondary complications.**
- **Alternative treatment/prevention during vaccine shortage.**

SUITABILITY OF TAMIFLU AS A PHARMACIST ONLY MEDICINE

Based on Tamiflu's positive risk / benefit ratio, the convenient oral dosage form and a pharmacist's ability to diagnose influenza with the appropriate tools, Tamiflu is a suitable medicine for Pharmacist distribution.

During a confirmed outbreak, clinical accuracy for determining that a patient is suffering from influenza using only a simple case definition is very high.
By utilising existing surveillance programmes we will be able to provide timely information to healthcare providers about levels of circulating influenza activity in the community.

When influenza is known to be circulating in the community clinical assessment of influenza is highly accurate with the aid of a simple case definition. Depending on the case definition applied, the results from several studies have shown that accuracy of diagnosis ranges from at least 60%, up to as high as 85%. Roche Products (New Zealand) Limited is proposing to develop and disseminate a simple diagnosis algorithm based on our clinical trial data and published information in our clinical trial programme. The following case definition showed a high degree of diagnostic accuracy when surveillance data indicated that influenza was prevalent.

Acute onset of:

- *respiratory symptoms such as cough, and*
- *high fever (>38°C)*

is likely to be associated with influenza infection.

The case definition will be proposed for incorporation into pharmacy protocols for Pharmacist Only Medicine Tamiflu, ensuring pharmacists will be provided with the necessary tool to identify influenza. The provision of influenza surveillance information significantly enhances the assessment of influenza (See Influenza Surveillance, 5.2). To minimize the likelihood of inappropriate use of Tamiflu Roche Products (New Zealand) Limited will work closely with pharmacy professional bodies to develop protocols for the diagnosis and treatment of influenza. Clear Guidelines, as mentioned in the previous section (i.e. Recognition of Influenza), will be provided. Accurate assessment of influenza is significantly improved when a prescriber is aware of the prevalence of influenza in the community

The decision to treat cannot be delayed until the presence of influenza can be confirmed by laboratory testing. The current point-of-care tests are variable in respect to specificity and sensitivity. A positive test is indicative of influenza, however a negative test cannot negate the presence of influenza. As such, clinical judgement and knowledge of the local surveillance data are required. In addition, accurate results are also dependant on adequate specimen collection and good sampling techniques. Due to the expense and variable specificity and sensitivity of point-of care tests their use in clinical practice is currently not cost effective.

Given that clinical accuracy of diagnosis when influenza is circulating using a case definition is often greater than 60%, treatment on the basis of clinical diagnosis is favoured over the test then treat strategy. Furthemore point-of-care testing has no value in the prophylaxis setting.

SAFETY AND RESISTANCE

Tamiflu is a medicine with hypersensitivity as it's only contraindication. In addition, interactions are limited. Tamiflu has an excellent safety profile with very few side effects. In clinical trials the most frequently reported adverse events were nausea and vomiting. These symptoms are transient and typically occur with the first dose. The data sheet also provides additional information on adverse effects that were observed during clinical trials. Post marketing experience has only led to the inclusion of very few additional adverse events in the product information, all of which occur rarely or very rarely. In addition, there has been no experience with overdose and as such Tamiflu has very low potential for abuse.

Drug resistance to Tamiflu is very uncommon. It is widely acknowledged that the development of the neuraminidase inhibitor antiviral agents was a break through for the treatment of influenza. A major concern for any drug that is designed to attack RNA viruses is the development of antiviral resistance. When the neuraminidase inhibitors first became available the excitement associated with the introduction of a novel tool to fight influenza infection was tempered by the rapid resistance that had developed to the earlier anti-influenza compounds, i.e. the M2 inhibitors. Neuraminidase Inhibitor Susceptibility Network (NISN) was set up in 1999 to oversee global surveillance. Their findings have shown that mutations conferring resistance to neuraminidase inhibitors occur very rarely, they are typically less virulent than wild-type viruses and they spread less easily. The incidence of viral resistance in samples derived from clinical isolates is about 2%, depending on viral subtype.

CONCLUSION

In conclusion, Tamiflu capsules are convenient, safe and effective in the treatment and prevention of influenza. The potential public health benefit has not been realised due to the limited window of opportunity for effective management option (treatment and prophylaxis). Tamiflu has an excellent safety profile that is consistent and stable with very few adverse characteristics making it appropriate for use as a Pharmacist Only Medicine. Improved access to Tamiflu will compliment the vaccination programme in an inter-pandemic situation and assist in the preparation for an influenza pandemic. In addition, public health benefits in the form of the reduced severity and complications contribute to a reduction in the economic and burden of influenza.